TABLE XXIV-11-2. Long-term results in patients with appendiceal carcinoid tumors treated by simple appendectomy only

Patients	*Follow-up* >5-yr.	>10-yr.
Total	110	86
Traced	108	83
Dead of known unassociated causes	2	5
Recurrent or metastatic carcinoid tumor	0	0

years. In an extensive review of the literature, only two reported incidences were found of metastasis occurring after treatment of carcinoid tumor of the appendix by appendectomy alone. Simple appendectomy, thus, is adequate treatment for patients with carcinoid tumors of the appendix that show no grossly recognizable evidence of metastasis. The only exception to this rule would be the uncommon case in which the tumor is 2 cm. or more in diameter. Such lesions should be regarded as aggressive carcinomas and treated accordingly.

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XXIV-12. *Large Bowel*

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In the cavity of the colon, was found a large portion of flesh, which, by its bulk, was the cause of impediment to the descent of faeces, and by a disorder of this kind, which was a consequence of that obstruction, the patient was carried off. Which cause being worthy of particular attention.

Record of a necropsy made on the body of Count de Caldarinis, a nobleman of Bologna.

John Baptista Cortesius, 1625[10]

Cancer of the large bowel (colon and rectum), afflicting as it does more patients than any other major malignant disease in the United States and most countries of Europe, is indeed worthy of particular attention. The specific types of malignant neoplasms originating in the colon and rectum are classified in Table XXIV-12-1. Over 98% of cancers of the large bowel are adenocarcinomas.

History. The quotation above represents one of the earliest gross pathologic descriptions of what in all likelihood was a carcinoma of the large bowel. Over a century later, in 1739, probably the first perineal resection of a rectal cancer was performed by Faget.[3] Reybard of Lyons is credited with the first successful resection of a colonic carcinoma in 1823. It is of interest that he performed a one-stage resection and primary anastomosis, but his method was severely criticized by the Paris Academy of

TABLE XXIV-12-1. Classification of cancer of the large bowel

- I. Carcinoma
  - A. Adenocarcinoma
  - B. Squamous cell carcinoma
  - C. Carcinoid tumor
- II. Sarcoma
  - A. Lymphoma
  - B. Leiomyosarcoma
  - C. Miscellaneous sarcomas

Exhibit D

[redacted]

TABLE XXIV-12-2. Segmental distribution of adenocarcinomas of the large bowel

Segment	*Percent**
Cecum	8.3
Ascending colon	5.7
Hepatic flexure	2.4
Transverse colon	5.6
Splenic flexure	5.5
Descending colon	11.4
Sigmoid	20.4
Rectum	40.7

*Based on 15,000 cases collected by Berk and Hauhrich.[3]

plasms are within range of the examining finger, and almost two-thirds can be visualized by the standard sigmoidoscope.

Grossly, adenocarcinomas of the large bowel are usually well demarcated from normal mucosa, and the classic appearance is that of a nodular, fungating mass with areas of ulceration surrounded by a considerable inflammatory reaction in the paracolonic tissues. They are hard in texture and yellow-gray on cut section. Scirrhous forms produce extremely firm tumors that usually involve only a short segment producing a napkin-ring appearance. Uncommonly, the scirrhous form may cover a long segment of the bowel, producing a "linitis plastica" appearance. About 20% of cases will be a mucinous or colloid form. These tumors are more common in the right colon and are usually soft, bulky, and friable. A papillary form is the malignant counterpart of the villous adenoma consisting of soft, friable fronds of epithelium. These tumors are usually found in the rectum. They are broad based and often encircle the lumen.

We have observed invasive bowel cancer to be grossly multicentric in 2.8% of 6012 cases studied, and an additional 1.7% developed second bowel cancers after an interval of six months or longer.[27] This tendency to multicentricity was markedly exaggerated in multiple polyposis and chronic ulcerative colitis.

Microscopically, carcinomas of the large bowel vary in differentiation from a close resemblance to normal mucosa to highly undifferentiated cells in sheets and cords that defy any attempt at recognition of the parent tissue. The Broder's system is frequently used to grade anaplasia, with grade I representing well-differentiated and grade IV highly undifferentiated morphologies. Mucus production is variable and may appear extracellularly or intracellularly in "signet ring" cells.

Pathogenesis and Spread. Of special interest are the recent contributions made by the cellular kineticist and cellular biologist to knowledge of the dynamic pathology of large bowel cancer.[24] By study of known premalignant conditions and mucosa adjacent to carcinoma, it has been possible to demonstrate transition states between normal epithelium and adenocarcinoma. Certain parameters of this "premalignant state" have been defined. In normal mucosa, cell division and DNA synthesis stop as the cells move through the midportions of the crypts. In premalignant states, the cells retain their ability to divide and make new DNA, with increasing numbers of these cells accumulating on the mucosal surface. Such cells have a greater ability to manufacture protein and have a higher thymidine kinase activity than the mature surface cell.

Cellular kinetic studies have also demonstrated that, in fact, the normal colonic mucosal cells reproduce more rapidly than do the cells of colonic adenomas or adenocarcinomas. The persistence of a tumor mass, therefore, seems to represent a failure of the constituent cells to mature and slough off rather than an accelerated rate of multiplication.

As the carcinoma of the large bowel advances, it spreads circumferentially in the bowel wall and into the paracolonic tissues, eventually encircling the bowel and causing clinical obstruction. Direct invasion by colonic tumors can involve any adjacent organ including stomach, duodenum, liver, pancreas, small bowel, kidney, spleen, retroperitoneal area, and abdominal wall. Local invasion produces the greatest clinical problem with rectal carcinomas. The almost immediately adjacent bladder, prostate, ureters, vagina, sacrum, and sacral nerves

may all become quickly involved in the neoplastic process rendering the tumor inoperable and producing devastating clinical syndromes.

From 39 to 68% of reported large bowel cancers encountered surgically have already shown metastasis to regional lymph nodes,[13] with the frequency of diagnosis of nodal involvement depending to a large extent on how meticulous the pathologist is in his search. Lymphatic spread from colonic tumors usually progresses in an orderly fashion from regional to mesenteric to aortic nodes. Rectal carcinomas may spread to inguinal nodes, or from obturator to iliac to para-aortic nodes. Once the thoracic duct has been reached by any of these routes, evidence of tumor may appear in the left supraclavicular nodes.

Although arterial walls seem to resist cancer invasion, the veins are exceedingly vulnerable. In several large surgical series of large bowel carcinomas, venous involvement has been reported in 15 to 61% of cases.[13] There is a strong correlation between this finding and later death with metastasis. Liver and lungs are overwhelmingly the most frequent sites of distant metastasis from large bowel cancer. Less common sites are bone, brain, adrenal glands, and kidneys.

Spread by implantation to peritoneum and abdominal wounds is also commonplace. Whether from implantation or unresected neoplasm, local recurrence frequently ensues after resection, and is observed more in lesions below the peritoneal reflection (23 to 34%) than in those above (4 to 11%).[13]

Death due to large bowel cancer results from the effect of distant metastasis (e.g., hepatic failure, cerebral metastases) in about 50% of patients, and from local recurrence effects (e.g., intestinal obstruction, ureteral obstruction, recurrence plus local sepsis) in the remaining 50%. In a study of 484 untreated patients with histologic confirmation of incurable large bowel cancer,[31] we found the mean duration of life from proof of unresectable cancer or metastasis to be 9.5 months (median 7.0 months) with a range of four weeks to over six years. As shown in Table XXIV-12-3, survival was slightly longer in the female and shorter in both the very young and the very old. The Broder's grade of anaplasia had a striking effect on survival, as did the extent of involvement with disease at the time of diagnosis of incurable cancer. Patients with previously indolent cancer, as evidenced by a longer interval from diagnosis of primary to diagnosis of metastasis, had a correspondingly longer survival after proof of incurable disease. Although undoubtedly in some measure artifactual, survival time was improved in patients whose primary lesion had been bypassed or resected.

Symptoms. Carcinoma of the large bowel usually is quite subtle in its early symptomatology. The minor change in bowel habit or the vague abdominal distress has usually been experienced by the patient before under benign and transient circumstances, and the occasional show of blood may be ascribed by the patient, and all too frequently by the physician, to hemorrhoids. A review of a number of large reported series of patients showed that the average duration from onset of symptoms to diagnosis ranged from 5.3 to 18 months.[3]

The nature of the symptomatology of large bowel cancer depends in large measure on the structure and function of the bowel at the site of tumor origin. The primary function of the right side of the colon is absorption of water and electrolytes, and the fecal content is usually liquid in consistency. Also, the bowel in this area is more distensible and has a greater diameter. Neoplasms here tend to be larger, fungating, and more friable. They are susceptible to ulceration and bleeding, but unless the tumor is immediately adjacent to the ileocecal valve, obstruction will be a very late manifestation. Except when bleeding is profuse, the blood will be unrecognized as it is incorporated in the fecal content. On the other hand, the primary function of the left colon and rectum is storage of solid fecal material, and the bowel diameter is smaller. Neoplasms here tend to be more scirrhous with early production of obstructive symptoms. Blood is usually grossly recognizable in the stool or